Remarks

The Examiner has rejected Claims 23-38 under 35 USC section 103(a) under a combination of GB2,228,262, US Patent 4,900,549, and WO99/27959 (itself having US 6,528,058 as a counterpart). The rejection is respectfully traversed.

A primary feature of the present invention is to provide adjuvant compositions that facilitate the triggering of substantial immune responses against an antigen (i.e. high antibody titers), while, at the same time, not being significantly reactogenic, therefore not to cause high and lingering irritancy at the site of vaccination. Such irritancy and reactogenic properties are of course painful to vaccinated animals, and even in the case of animals soon to be slaughtered, such effects compromise carcass/meat characteristics.

According to the practice of the present invention, such non-obvious results (see Examples 5-7 in the Specification) are provided via adjuvant compositions that consist essentially of an ionic polysaccharide and an immunostimulating complex (as specially defined herein) which itself comprises a saponin and a sterol (such as cholesterol), and wherein the immunostimulating complex may contain additional active components. Such features are neither present or predicted by the prior art, and any accidental overlap therewith has been removed by replacing the term "comprising" with the term "consisting essentially of" at the specific appropriate point in Claim 23.

Prior to addressing the specific points of the Examiner's rejection, some overall comments concerning the cited prior art references are in order.

The WO99/27959 reference is directed to trivalent adjuvant compositions which those authors state (see page 10) provide for higher antibody titers that certain cited divalent adjuvant compositions, although there may not be appropriate comparison also as to reactogenic properties of the various adjuvants. In any case, the compositions disclosed according to this reference invariably contain an immunoadjuvant oil as a necessary ingredient, and never contain cholesterol (complexed with saponin according to the practice of the present invention to prevent the saponin from "extracting" native cholesterol molecules from cell membranes thus causing localized tissue damage at the injection site). Therefore, it is difficult to imagine how this reference is to be combined with any other teachings, in order to provide a proper section 103 rejection, absent a specific teaching *from some other reference* that the essential ingredient (adjuvating oil) of WO99/27959 is NOT to

be used after all.

The GB 2 228 262 publication is solely directed to LHRH (or LHRH analog) conjugates which may be further coupled to DT, for example. However, the present Applicant does not claim to be the first inventive entity to have ever coupled LHRH to DT, and present claim 23 is not limited in any way as to the antigen which is delivered with the adjuvant composition therewith, therefore the overall relevance of the cited publication to the present invention seems quite remote.

In regard of US 4,900, 549 (and there are other references which report similar technology), and although the reference is directed to providing "immunostimulatory complexes", there is no teaching at all in this reference that the adjuvant can be improved (i.e. to provide a preferred combination of high immunizing activity and reduced reactogenicity) by replacing some of the saponin/immunostimulatory complex with ionic polysaccharide. As previously mentioned, this missing teaching is clearly not to be provided by WO99/27959, which *invariably* instructs to also use an adjuvating oil, all the while the saponin is not formed into an immunostimulatory complex, as the present application (and claims) so define.

Therefore, in regard of how all such teachings might be combined, the following further comments are of note.

Applicant does not understand the purpose of the citation to GB 2,228,262, since most of what is taught according to the practice of that invention is simply not present according to the practice (independent claim 23) of the present invention, and the present Applicant does not include alum as an adjuvant at all. The Examiner acknowledges that everything that is the present in Applicant's adjuvant is physically missing from that reference (see Page 2, numbered Para 5 of the Official Action),

Applicant respectfully disagrees with the Examiner's assertion that the WO99/27959 reference teaches (again see Page 2, numbered Para 5, of the Official Action) that DEAE-dextran and Quil A are a synergistic combination, since the actual disclosed compositions also require oil as additional adjuvant to achieve this apparent synergy, and the very text of the publication states that the specifically-identified 3 component adjuvant systems work better than 2 component systems. There is simply no statement or data to the contrary. Further, there is no mention of the value of cholesterol as an added component, both to place

the saponin in an immunostimulatory complex, and also to minimize saponin-triggered cell damage. Therefore, the combination of WO99/27959 and GB 2,228,262 simply does not suggest the present invention.

To the extent that the '549 patent is supposed to bridge this deficiency, it is noteworthy that the Official Action only devotes 2 lines of text to it (see Page 3), and no discussion is presented (either in the references or the Official Action) as to how those skilled in the art are first supposed to recognize, but then disregard, the teaching in WO99/27959 of obligate adjuvant oil component.

The mere existence of the various components of the present invention -- as separate components in the separate prior art citations -- is not the same as the motivation to combine them. And notwithstanding that the teaching of effectiveness in the WO99/27959 publication is actually and clearly related to the oil-containing, 3-component adjuvant and not a 2-component (Quil A and DEAE-dextran) adjuvant [as reported on Page 5 of the Official Action], there simply remains the requirement that the references must be considered for the totality of what they teach, and not for any convenient bits and pieces of information therein.

The '549 patent cannot be read to mean that all possible saponin-containing systems are substantially improved by adding cholesterol, both as to reactogenicity and immunogenicity. There is simply no support for this interpretation of the reference. In any case, the "parallel" teaching of the WO99/27959 publication is simply that cholesterol-free saponin systems can be improved by adding ionic polysaccharide, but only if adjuvating oil is also present.

Fundamentally, the Patent Office cannot pick and choose which among all the items of information in the respective references are to be exploited, and which teachings (or lack of teachings) are to be conveniently disregarded, in an attempt to reconstruct the present Applicant's invention. Thus, it is impossible to read the references, in their entirety, to suggest that one should make a saponin-ionic polysaccharide system, but that you should certainly add cholesterol, and certainly leave out any adjuvating oil.

On this basis, Applicant's invention is both novel and non-obvious.

Conclusion

The Examiner is welcome to contact the undersigned to facilitate further prosecution. A Petition for Extension of Time (in duplicate) is attached, and any needed fees may be charged to Applicant's Deposit Account, No. 16-1445. An early and favorable action is respectfully requested.

Respectfully submitted,

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